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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/643,226

08/19/2003

Ashley I. Bush

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04/29/2008

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EXAMINER

DUTT, ADITI

ART UNIT

PAPER NUMBER

1649

MAIL DATE

DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/643,226	<b>Applicant(s)</b> BUSH ET AL.	
	<b>Examiner</b> Aditi Dutt	<b>Art Unit</b> 1649	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 31 January 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 36,37 and 39-42 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 36,37 and 39-42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Claims***

1. The amendment filed on 31 January 2008 has been entered into the record and has been fully considered. Claims 36 and 42 are amended.
2. Claims 36-37, 39-42, drawn to a method of identification of an agent that inhibits the redox reactive metal-mediating cross-linking of A $\beta$  (amyloid beta peptide), are being considered in the instant application.
3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicants response and withdrawn.
4. Applicant's arguments filed on 31 January 2008 have been fully considered. New grounds of objection and rejection are as follows.

### ***Response to Amendment***

#### ***Claim rejections/objections maintained/new grounds of rejection***

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (31 January 2008).
6. Upon consideration of Applicant's amendments and arguments, rejection of claims 36-37 and 39-42 under 35 U.S.C, 112, second paragraph is withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The rejection of claims 36, 39, 40 and 41, under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. (Journal of Biological Chemistry 267, page 18210-18217, 1992), in view of Bush et al. (Science 265: 1464-1467, 1994), and Mantyh et al. (J Neurochem 61: 1171-1174, 1993) is being applied to the amended claims for reasons of record in the Office Action dated 31 October 2007.
8. Applicants disagree with the Office's rejection because (i) one of ordinary skill in the art would not have been motivated to combine the teachings of Dyrks et al regarding A4CT to the teachings of Bush et al or Mantyh et al regarding A $\beta$ , because of different oxidative properties of A4CT and A $\beta$ , and (ii) the references cited in the rejection do not teach or suggest screening methods for a candidate agent that inhibit redox-reactive metal mediated cross linking of A $\beta$ . Referring to the 1.132 Declaration filed on 10 October 2006, Applicants further assert that "different oxidation modification are likely responsible for the observed hemoglobin and H<sub>2</sub>O<sub>2</sub>-induced aggregation of A4CT and A $\beta$  in Dyrks et al."

Because Dyrks et al. do not teach the claimed method of inhibiting metal mediated A $\beta$  cross-linking using a candidate agent, there is no motivation to combine the teachings of Dyrks et al with Bush et al and Mantyh et al. to arrive at the present claims. Furthermore, Applicants argue that the references do not teach or suggest candidate agents or screening methods at all. Because the references do not cite these two basic elements of the instant claims, Applicants assert that a *prima facie* case of obviousness cannot be established.

9. Applicants' arguments directed to the above rejection are fully considered but have not been found to be persuasive. Although the Office does not disagree to Applicant's statements regarding "differing arrays of oxidatively modified products" that are "likely to be generated by metal catalyzed oxidation of A4CT and A $\beta$ ", the claims recite "A $\beta$ ", which is broadly defined as comprising "of peptides A $\beta$ 1-39, A $\beta$ 1-40, ..... and mixtures thereof" in the instant specification (page 14, lines 24-26)". Because "A $\beta$ " comprises many peptides of differing lengths, and A4CT of Dyrks et al. include A $\beta$ , the teachings in the reference are commensurate with the instant claims (emphasis added). Therefore, it would have been obvious for the person of ordinary skill in the art at the time the claimed invention was made, to modify inhibiting the FeCl<sub>2</sub> induced A4CT cross-linking with agents like ascorbic acid or vitamin E, as taught by Dyrks et al., to inhibiting metal induced aggregation of A $\beta$  peptide as taught by Bush et al. or Mantyh et al. The person of ordinary skill would have used the above method for the identification of an agent with a reasonable expectation of success, because

the prior art teaches that A $\beta$  isoforms (such as A $\beta$ 1-40), produced by cleavage of the amyloid precursor protein are implicated in the plaque formation in disease states like Alzheimer's Disease, and the method of inhibiting the formation of metal induced aggregates by agents such as antioxidants or chelators was well known in the art. Additionally, the metal induced aggregation of A $\beta$  peptide is very relevant in vivo, e.g. in the CSF, which contains a concentration of  $\sim 6 \times 10^{-10}$  M of the peptide. Furthermore since the instant claims are directed to a method encompassing specific steps for the identification of a candidate agent, and since the combined references teach the claimed method steps as discussed above, the claimed invention as a whole stays *prima facie* obvious over the combined teachings of the prior art. Additionally, since the candidate agent is only identified by its property of inhibiting metal mediated cross-linking, and since this is elicited by ascorbic acid, and vitamin E derivative in the Dyrks reference, these compounds inherently function as candidate agents and the references teach the claimed method.

10. The rejection of claims 36, 39-42, under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. (Journal of Biological Chemistry 267, page 18210-18217, 1992), in view of Bush et al. (Science 265: 1464-1467, 1994), and Mantyh et al. (J Neurochem 61: 1171-1174, 1993) is being applied to the amended claims for reasons of record in the Office Action dated 31 October 2007.

11. Applicants allege that as explained above, one of ordinary skill in the art would not be motivated to combine the teachings of Dyrks et al (referring A4CT) with Bush et al and Mantyh et al. (referring to A $\beta$ ) due to (i) different oxidative properties, and (ii) no teaching or suggestion in any of the references with regards to methods for a candidate agent, or an agent.

12 Applicants' arguments directed to the above rejection have been fully considered but have not been found to be persuasive. For reasons detailed above, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art. It is reiterated that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to look for the presence or absence of  $\beta$ A4 cross-linking as disclosed by Dyrks et al, Bush et al., or Mantyh et al., for the purpose of identifying an agent that inhibits metal-mediated cross linking of  $\beta$ A4 peptides, using Western blot assay with a reasonable expectation of success.

### ***Conclusion***

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.**

15. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

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calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.
17. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD

18 April 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649